

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/012719 A1

(51) International Patent Classification⁷: A61K 9/70, 31/38

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:

PCT/EP2003/008319

(22) International Filing Date: 28 July 2003 (28.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02016864.7 30 July 2002 (30.07.2002) EP

(71) Applicant: SCHWARZ PHARMA AG [DE/DE]; Alfred-Nobel-Strasse 10, 40789 Monheim (DE).

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/012719 A1

(54) Title: IMPROVED TRANSDERMAL DELIVERY SYSTEM

(57) Abstract: An improved Transdermal Delivery System (TDS) comprising a backing layer inert to the components of the matrix, a self-adhesive matrix containing an amine-functional drug and a protective foil or sheet to be removed prior to use, characterized in that the self-adhesive matrix consists of a solid or semi-solid semi-permeable polymer (1) wherein an amine functional drug in its free base form has been incorporated, (2) which is saturated with the amine functional drug and contains said drug as a multitude of microreservoirs within the matrix, (3) which is highly permeable for the free base of the amine functional drug, (4) which is impermeable for the protonated form of the amine functional drug, (5) wherein the maximum diameter of the microreservoirs is less than the thickness of the matrix. Said TDS provides for enhanced flux of the amine functional drug across the TDS/skin interface.

Improved Transdermal Delivery System

FIELD OF INVENTION

5 The present invention relates to an improved transdermal delivery system for amine functional drugs. Moreover, the invention relates to a method of treatment using the transdermal delivery system.

TECHNICAL BACKGROUND

To date, various transdermal delivery systems (TDS) for the administration of amine functional drugs, such as rotigotine and many others, have been described. WO 94/07568 discloses 5 a TDS containing rotigotine hydrochloride as active substance in a two-phase matrix, which is essentially formed by a hydrophobic polymer material as the continuous phase and a disperse hydrophilic phase contained therein and mainly containing the drug and hydrated silica. The silica is said 10 to enhance the maximum possible loading of the TDS with the hydrophilic salt. Moreover, the formulation of WO94/07568 usually contains additional hydrophobic solvents, permeation 15 promoting substances dispersing agents and, in particular, an emulsifier which is required to emulsify the aqueous solution 20 of the active component in the lipophilic polymer phase. A 25 TDS prepared by using such a system has been tested in healthy subjects and Parkinson's patients. However, no satisfactory drug plasma levels were achieved.

30 Various further TDS have been described in WO99/49852. The TDS used in this patent application comprises a backing layer, inert with respect to the constituents of the matrix, a self-adhesive matrix layer containing an effective quantity 35 of rotigotine hydrochloride or rotigotine, which contains a substantial amount of rotigotine hydrochloride (>5 % w/w), and a protective film, which is to be removed before use. The matrix system is composed of a non-aqueous polymer

adhesive system, based on acrylate or silicone, with a solubility of rotigotine of at least 5% w/w. Said matrix has been described as being essentially free of inorganic silicate particles. However, even the TDS described in 5 WO99/49852 leave something to be desired as regards the obtainable flux rates of drug across human skin.

In the TDS according to WO94/07568 and many related applications, passive diffusion membranes were used.

10

However, as the skin is to be seen as a very efficient barrier for most drug candidates, such type of membrane controlled systems are more or less limited in practice to transdermal delivery of active substances that reveal a very 15 high skin permeability. Additionally, special requirements on drug release kinetics have to be met like contact delivery over several days.

An object of the present invention is to control (i.e. to 20 canalise/manoeuvre) the transport of a drug substance towards and across the skin from a drug reservoir, thereby enhancing the flux of the drug substance across the TDS/skin interface.

A further object and aspect of the present invention is to 25 provide a suitable composition and manufacturing methods of polymer matrices in TDS which lead to an enhanced delivery of weakly basic amines to and across the skin by

- 30 (i) preventing back diffusion of the drug portion which is ionized in the skin according to its pKa value - from the skin tissue into the TDS,
- 35 (ii) offering continuous delivery of the active compound across the stratum corneum not only via the common more lipophilic route (e.g. intercellular) but also through hydrophilic pores (e.g. eccrine sweat glands).

SUMMARY OF THE INVENTION

These objects are solved by providing a TDS comprising a backing layer inert to the components of the matrix, a self-
5 adhesive matrix containing an amine functional drug and a protective foil or sheet to be removed prior to use,

characterized in that

10 the self-adhesive matrix consists of a solid or semi-solid semi-permeable polymer

- (1) wherein an amine functional drug in its free base form has been incorporated,
- 15 (2) which is saturated with the amine functional drug and contains said drug as a multitude of microreservoirs within the matrix,
- (3) which is highly permeable for the free base of the amine functional drug,
- 20 (4) which is impermeable for the protonated form of the amine functional drug,
- (5) wherein the maximum diameter of the microreservoirs is less than the thickness of the matrix.

25

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the effect of the protonation of the drug in the semi-permeable matrix on the drug absorption.

30

Fig. 2 shows the impact of the size distribution of the microreservoirs in the semi-permeable matrix on the drug absorption.

35

Fig. 3 shows the effect of reducing the amount of the protonated form of the drug in the semi-permeable matrix and

reducing the size of the microreservoirs on the drug absorption.

Fig. 4 shows a microscope image of a conventional TDS.

5

Fig. 5 shows a microscope image of the TDS according to the invention.

Fig. 6 shows the effect of reducing the amount of the protonated form of the drug in the semi-permeable matrix and reducing the size of the microreservoirs on the in vitro skin permeation of the drug.

Fig. 7 shows a comparison of the in vitro skin permeation of the drug for the TDS of the invention and an acrylate-based TDS.

DESCRIPTION OF THE INVENTION

30 The present invention provides a TDS for amine functional drugs providing a high steady state flux rate of the amine functional drug over the TDS/skin interface.

Surprisingly, it was found that drug release properties of a
25 TDS having a silicone-type adhesive matrix containing an amine functional drug can be significantly enhanced by

- 30 (1) minimizing the amount of the amine functional drug which is present in the protonated form (salt form);
- (2) incorporating the amine functional drug in a multitude of microreservoirs within the self-adhesive matrix consisting of a solid or semi-solid semi-permeable polymer.

35

The impact of above described measures on drug release characteristics of rotigotine in vivo is illustrated in

Figs. 1, 2 and 3. The relative drug absorption *in vivo* was highest for the sample according to the invention; increase of the size of the microreservoirs and/or the amount of drug salt residues in the TDS led to slower initial drug release.

5

Based on the above findings, the present invention was accomplished.

When using the TDS, according to the present invention, a high transfer of the amine functional drug from the silicone matrix into the outermost skin layer can be achieved. Consequently, plasma values of the amine functional drug are sufficient to allow for a reasonable expectation that an efficient treatment with these drugs with fewer side effects 5 can be provided.

It should be understood that the term "treatment" in the context of this application is meant to designate a treatment or an alleviation of the symptoms of the diseases that can be treated with the amine functional drugs useful in this invention. The treatment may be of a therapeutic or prophylactic nature.

In a preferred embodiment the amine functional drug 5 incorporated in the TDS of the present invention has an octanol/water partitioning coefficient $\log P \geq 2.8$ at pH 7.4. In another preferred embodiment the amine functional drug has a pK_a of 7.4 to 8.4. In an especially preferred embodiment the amine functional drug has an octanol/water partitioning coefficient $\log P \geq 2.8$ at pH 7.4 and a pK_a of 7.4 to 8.4. 0 The pK_a value can be measured by standard methods. A particularly preferred method is potentiometric titration of aqueous drug solutions (without addition of organic cosolvents) at room temperature.

5

The octanol/water partitioning coefficients (octan-1-ol/water partitioning coefficients) are determined at pH 7.4, 37°C and

an ionic strength of 0.15 in an appropriate buffer solution according to the method described by E. Miyamoto et al. (E. Miyamoto et al. "Physico-chemical Properties of Oxybutynin" Analyst (1994), 119, 1489-1492).

5

Particularly preferred amine functional drugs are dopamine D2 agonists, which are useful for example in the treatment of Parkinson's disease. Especially preferred dopamine D2 receptor agonists are aminotetraline compounds, such as 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol (INN: rotigotine).

Other examples for particularly preferred amine functional drugs are N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-propanamide (INN: fentanyl) which is useful in the treatment of pain and anticholinergic drugs exerting an antispasmodic effect on smooth muscles and inhibiting the muscarinic action of acetylcholin on smooth muscles. Examples of such anticholinergic drugs which are useful in the present invention are 4-diethylamino-2-butynyl phenylcyclohexyl-glycolate (INN: oxybutynine) and 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate (INN: fesoterodine). Oxybutynine and fesoterodine are useful in the treatment of urinary incontinence.

25

It will be understood by a person skilled in the art that the amine functional drugs, such as rotigotine, fentanyl, oxybutynine and fesoterodine, may all exist in various isomeric forms. It has to be understood that in this case the amine functional drug may be any single isomer or a mixture of different isomers. If the amine functional group contains asymmetric carbon atoms, any single enantiomer or a mixture of enantiomers may be used. Rotigotine, fentanyl, oxybutynine and fesoterodine all contain one asymmetric carbon atom. Hence, the S- or R-enantiomer or the racemate or any other enantiomer mixture of these compounds may be used as the amine functional drug.

At least a part of the amine functional drug is contained in a multitude of microreservoirs distributed within the self-adhesive matrix of the TDS according to the invention. This does not exclude and will normally even imply that a certain fraction of the amine functional drug is dissolved in the solid or semi-solid semi-permeable polymer of the matrix at its saturation concentration.

0 Within this specification "microreservoirs" are meant to be understood as particulate, spatially and functionally separate compartments consisting of pure drug or a mixture of drug and crystallization inhibitor, which are dispersed in the self-adhesive (polymer) matrix. Preferably the self-adhesive matrix contains 10^3 to 10^9 microreservoirs per cm^2 of its surface, particularly preferred are 10^6 to 10^9 microreservoirs per cm^2 .

The amine functional drug is incorporated in the self-adhesive matrix in its free base form. This does not totally exclude the presence of some residual salt form of the amine functional drug in the final TDS. However, the salt form of the amine functional drug should be contained in the self-adhesive matrix of the final TDS in an amount of preferably less than 5 %, more preferably less than 2 %, particularly less than 1 % (w/w).

If the amine functional drug is present in the self-adhesive matrix in its protonated (salt) form, it will not be released by the self-adhesive matrix. Thus, the amount of the salt form of the amine functional drug can be determined by performing a drug dissolution test according to the Paddle over Disk method as described in the United States Pharmacopoeia (United States Pharmacopoeia/New Formulary (USP25/NF20), Chapter 724 "Drug Release", United States Pharmacopoeial Convention, Inc., Rockville, MD 20852, USA (2002)), using the following conditions: dissolution medium:

900 ml phosphate buffer pH 4.5; temperature adjusted to 32 ± 0.5°C; paddle rotation speed: 50 rpm; sampling times: 0.5, 1, 2 and 3 h, respectively. The increase in the eluted drug concentration can be used to calculate the amount of 5 unprotonated drug in the matrix.

The amount of the salt form of the amine functional drug may be reduced e.g. by reducing the water content of the mass containing the drug and organic solvent(s). In a 0 particularly preferred embodiment of the invention the water content is reduced during manufacture to preferably less than 0.4 % (w/w), more preferably less than 0.1 %, of the mass.

A further step, which may be taken for reducing the amount of 5 the salt form of the amine functional drug, is isolating the free base form of the amine functional drug in solid form prior to the preparation of the TDS. If the free base of the amine functional drug is produced in situ during the manufacture of the TDS by neutralizing an acid addition salt, 10 a certain residue of the ionized drug form will remain in the polymer matrix (usually > 5 % (w/w) and up to approximately 10 %). Therefore, such in situ preparation of the free base form will generally not be suitable for practising the present invention.

15 The maximum diameter of the microreservoirs is less than the thickness of the matrix, preferably up to 70 % of the thickness of the matrix, particularly preferably 5 to 60 % of the thickness of the matrix. For an exemplary thickness of 20 the matrix of 50 µm this corresponds to a maximum diameter of the microreservoirs in the range of preferably up to 35 µm. The term "maximum diameter" is meant to be understood as the diameter of the microreservoirs in one dimension (x-, y-, or z-dimension), which is the largest. It is clear to the 25 skilled person that in case of spherical diameters the maximum diameter corresponds to the microreservoir's diameter. However, in the case of microreservoirs, which are

not shaped in the form of spheres - i.e. of different geometric forms -, the x-, y- and z-dimensions may vary greatly.

5 As the maximum diameter of the microreservoirs in the direction of the cross-section of the matrix, i.e. between the release surface and the backing layer, is less than the thickness of the matrix, direct contact between the skin and the basic microreservoirs containing the amine-functional
10 drug is avoided, if not at all prevented. Owing to the slightly acidic pH of the skin, direct contact between the skin and the microreservoirs in the matrix leads to protonation of the amine-functional drug, thereby deteriorating the semi-permeability of the matrix.

15 In a particularly preferred embodiment of the invention, the mean diameter of the microreservoirs containing the amine functional drugs distributed in the matrix is in the range of 1 to 40 %, even more preferably 1 to 20 %, of the thickness
20 of the drug-loaded self-adhesive matrix. For an exemplary thickness of the matrix of 50 μm this corresponds to a mean diameter of the microreservoirs in the range of preferably 0.5 to 20 μm . The term "mean diameter" is defined as the mean value of the x,y,z-average diameters of all
25 microreservoirs. The target particle size can be adjusted by the solids content and viscosity of the drug-containing coating mass.

30 The maximum and mean diameters of the microreservoirs as well as the number of microreservoirs per surface area of the self-adhesive matrix can be determined as follows: The release liner is removed from the TDS, and the free adhesive surface is examined with a light microscope (Leica microscope type DM/RBE equipped with a camera type Basler A 113C). The
35 measurement is performed by incidental polarized light analysis using a microscope at 200x magnification. A picture analysis is performed using the software Nikon Lucia_Di,

Version 4.21, resulting in mean and maximum diameters for each sample.

The TDS of the present invention is of the "matrix" type. In such matrix type TDS the drug is dispersed in a polymer layer. The TDS of the matrix type in their simplest version comprise a one-phase (monolayer) matrix. They consist of a backing layer, a self-adhesive matrix containing the active agent and a protective foil or sheet, which is removed before use.

Versions that are more complicated comprise multi-layer matrixes, wherein the drug may be contained in one or more non-adhesive polymer layers. The TDS of the present invention is preferably a one-phase (mono layer) matrix system.

The solid or semi-solid semi-permeable polymer of the self-adhesive matrix has to satisfy the following requirements:

1. Sufficient solubility and permeability for the free base form of the amine functional drug.
2. Impermeability for the protonated form of the amine functional drug.

In a particular preferred embodiment of the invention the self-adhesive matrix is free of particles that can absorb salts of the amine functional drug on the TDS/skin interface.

Examples of particles that can absorb salts of the amine functional drug on the TDS/Skin interface include silica. Such particles that can adsorb salts of the amine functional drug may represent diffusion barriers for the free base form of the drug and may result in the formation of channels inducing some permeability of the self-adhesive matrix for the protonated form of the drug. Such embodiments are therefore disadvantageous for practising the invention.

The self-adhesive matrix of the TDS of the present invention consists of a solid or semi-solid semi-permeable polymer. Usually this polymer will be a pressure sensitive adhesive (PSA) or a mixture of such adhesives. The pressure sensitive adhesive(s) form a matrix in which the active ingredient and the other components of the TDS are incorporated.

The adhesive used in the present invention should preferably be pharmaceutically acceptable in a sense that it is biocompatible, non-sensitising and non-irritating to the skin. Particularly advantageous adhesives for use in the present invention should further meet the following requirements:

- 5 1. Retained adhesive and co-adhesive properties in the presence of moisture or perspiration, under normal temperature variations,
- 10 2. Good compatibility with the amine functional drug, as well as with the further excipients used in the formulation.

Although different types of pressure sensitive adhesive may be used in the present invention, it is preferred to use lipophilic adhesives having both a low drug and low water absorption capacity. Particular preferably, the adhesives have solubility parameters which are lower than those of the amine functional drugs. Such preferred pressure sensitive adhesives for use in the TDS of the present invention are silicone type pressure sensitive adhesives. Especially preferred pressure sensitive adhesives for use in the TDS of the invention are of the type forming a soluble polycondensed polydimethylsiloxane (PDMS) / resin network, wherein the hydroxy groups are capped with e.g. trimethylsilyl (TMS) groups. Preferred adhesives of this kind are the BIO-PSA silicone pressure sensitive adhesives manufactured by Dow

Corning, particularly the Q7-4201 and Q7-4301 qualities. However, other silicone adhesives may also be used.

In a further and especially preferred aspect, two or more
5 silicone adhesives are used as the main adhesive components. It can be advantageous if such a mixture of silicone adhesives comprises a blend of high tack silicone pressure sensitive adhesive comprising polysiloxane with a resin and a medium tack silicone type pressure sensitive adhesive
.0 comprising polysiloxane with a resin.

Tack has been defined as the property that enables an adhesive to form a bond with the surface of another material upon brief contact under light pressure (see e.g. "Pressure
.5 Sensitive Tack of Adhesives Using an Inverted Probe Machine", ASTM D2979-71 (1982); H.F. Hammond in D. Satas "Handbook of Pressure Sensitive Adhesive Technology" (1989), 2nd ed., Chapter 4, Van Nostrand Reinhold, New York, page 38).

20 Medium tack of a silicon pressure sensitive adhesive indicates that the immediate bond to the surface of another material is weaker compared to high tack silicon adhesive. The mean resin/polymer ratio is approx. 60/40 for medium tack adhesives, whereas it is approx. 55/45 for high tack
25 adhesives. It is known to the skilled person that both tape and rheological properties are significantly influenced by the resin/polymer ratio (K.L. Ulman and R.P. Sweet "The Correlation of Tape Properties and Rheology" (1998), Information Brochure, Dow Corning Corp., USA).

30 Such a blend comprising a high and a medium tack silicone type pressure sensitive adhesive comprising polysiloxane with a resin is advantageous in that it provides for the optimum balance between good adhesion and little cold flux.
35 Excessive cold flux may result in a too soft patch which easily adheres to the package or to patient's garments. Moreover, such a mixture seems to be particularly useful for

obtaining higher plasma levels. A mixture of the aforementioned Q7-4201 (medium tack) and Q7-4301 (high tack) proved to be especially useful as a matrix for the TDS according to the present invention.

5 In a further preferred embodiment, the TDS further includes a crystallization inhibitor. Several surfactants or amphiphilic substances may be used as crystallization inhibitors. They should be pharmaceutically acceptable and 0 approved for use in medicaments. A particularly preferred example of such a crystallization inhibitor is soluble polyvinylpyrrolidone, which is commercially available, e.g. under the trademark Kollidon® (Bayer AG). Other suitable crystallization inhibitors include copolymers of 5 polyvinylpyrrolidone and vinyl acetate, polyethyleneglycol, polypropyleneglycol, glycerol and fatty acid esters of glycerol or copolymers of ethylene and vinyl acetate.

The device of the present invention further comprises a 10 backing layer, which is inert to the components of the matrix. This backing layer is a film being impermeable to the active compounds. Such a film may consist of polyester, polyamide, polyethylene, polypropylene, polyurethane, polyvinyl chloride or a combination of the aforementioned 15 materials. These films may or may not be coated with an aluminium film or with aluminium vapour. The thickness of the backing layer may be between 10 and 100 µm, preferably between 15 and 40 µm.

20 The TDS of the present invention further comprises a protective foil or sheet, which will be removed immediately prior to use, i.e. immediately before the TDS will be brought into contact with the skin. The protective foil or sheet may consist of polyester, polyethylene or polypropylene which may 25 or may not be coated with aluminium film or aluminium vapour or fluoropolymers. Typically the thickness of such a protective foil or sheet ranges from between 50 and 150 µm.

So as to facilitate removal of the protective foil or sheet when wishing to apply the TDS, the protective foil or sheet may comprise separate protective foils or sheets having overlapping edges, similar to the kind used with the majority 5 of conventional plasters.

In a preferred embodiment of the present invention, the TDS has a basal surface area of 5 to 50 cm², particularly of 10 to 30 cm². It goes without saying that a device having a 0 surface area of, say, 20 cm² is pharmacologically equivalent to and may be exchanged by two 10 cm² devices or four 5 cm² devices having the same drug content per cm². Thus, the surface areas as indicated herein should be understood to refer to the total surface of all devices simultaneously 5 administered to a patient.

Providing and applying one or several TDS according to the invention has the pharmacological advantage over oral therapy that the attending physician can titrate the optimum dose for 10 the individual patient relatively quickly and accurately, e.g. by simply increasing the number or size of devices given to the patient. Thus, the optimum individual dosage can often be determined after a time period of only about 3 weeks with 15 low side effects.

20 A preferred content of the amine functional drug in the TDS according to the invention is in the range of 0.1 to 2.0 mg/cm². Still more preferred are 0.20 to 1.0 mg/cm². If a 25 7 day patch is desired, higher drug contents will generally 30 be required.

The device used in the present invention is preferably a patch having a continuous adhesive matrix in at least its center portion containing the drug. However, transdermal 35 equivalents to such patches are likewise comprised by the present invention, e.g. an embodiment where the drug is in an inert but non-adhesive matrix in the center portion of the

device and is surrounded by an adhesive portion along the edges.

The TDS according to the present invention is prepared by a manufacturing process, which comprises preparing a drug loaded adhesive, coating, drying or cooling and lamination to get the bulk product, converting the laminate into patch units via cutting, and packaging.

0 The invention and the best mode for carrying it out will be explained in more detail in the following non-limiting examples.

INVENTION EXAMPLE 1 (very low salt content, small
.5 microreservoirs)

252.6 g Rotigotine free base are dissolved in 587.8 g ethanol 100 % w/w and mixed with 222.2 g ethanolic solution containing 25 % w/w polyvinylpyrrolidone (Kollidon F 90), 0.11 % w/w aqueous sodium bisulfite solution (10 % w/w), 0.25 % ascorbyl palmitate and 0.62 % DL- α -tocopherol. To the homogenous mixture 1692.8 g BIO-PSA Q7 4301 (73 % w/w), 1691.6 g BIO-PSA Q7 4201 (73 % w/w) and 416.3 g petrol ether are added and all components are stirred for at least 1 hour to get a homogenous dispersion.

For manufacture of the patch matrix, the dispersion is coated onto a suitable release liner (for example Scotchpak 1022) and the solvents are continuously removed in a drying oven at temperatures up to 80°C to get a drug-containing adhesive matrix of 50 g/m² coating weight. The dried matrix film is laminated with a polyester-type backing foil which is siliconized on the inner side and aluminium vapor coated on the opposite side.

35

The individual patches are punched out of the complete laminate and are sealed into pouches under a nitrogen flow.

The rotigotine contained in the matrix was quantitatively released after 3 hours in the drug dissolution test according to the Paddle over Disk method as described in the USP using 5 the conditions as described above. This result indicates that the obtained TDS was completely free of rotigotine hydrochloride.

The mean size of the microreservoirs in the TDS was approx. 0 10 μm with typical sizes in the range of 5 to 35 μm . A microscope image of the obtained TDS is shown in Fig. 5.

COMPARATIVE EXAMPLE 1 (high salt content, small
microreservoirs)

.5 2400 g Rotigotine hydrochloride were added to a solution of 272.8 g NaOH in 3488 g ethanol (96 %). The resulting mixture was stirred for approximately 10 minutes. Then 379.2 g of sodium phosphate buffer solution (27.6 g $\text{Na}_2\text{HPO}_4 \times 2\text{H}_2\text{O}$) and 10 53.2 g $\text{NaH}_2\text{PO}_4 \times 2\text{H}_2\text{O}$ in 298.5 g water) was added. Insoluble or precipitated solids were separated from the mixture by filtration. The filter was rinsed with 964 g ethanol (96 %) to obtain a particle-free ethanolic solution of rotigotine essentially in the form of the free base.

25 The rotigotine solution (6150 g) in ethanol (30 % w/w) was mixed with 407 g ethanol (96 %). The resulting solution was mixed with 1738.8 g of an ethanolic solution containing 25 wt.% polyvinylpyrrolidone (Kollidon[®] 90F), 0.11 wt.% 30 aqueous sodium bisulfite solution (10 wt.%), 0.25 wt. % ascorbyl palmitate, and 0.62 wt.% DL-alpha-tocopherol until homogeneity. To the mixture 13240 g of an amine resistant high tack silicone adhesive (BIO-PSA[®] Q7-4301 mfd. by Dow Corning) (73 wt.% solution in heptane), 13420 g of an amine 35 resistant medium tack silicone adhesive (BIO-PSA[®] Q7-4201 mfd. by Dow Corning) (72 wt.% solution in heptane), and 3073

g petrol ether were added, and all components were stirred until a homogenous dispersion was obtained.

The dispersion was coated onto a suitable polyester release liner (SCOTCHPAK® 1022) with a suitable doctor knife and the solvents were continuously removed in a drying oven at temperatures up to 80°C for about 30 minutes to obtain a drug containing adhesive matrix of 50 g/m² coating weight. The dried matrix film was laminated with a polyester-type backing foil (SCOTCHPAK® 1109). The individual patches were punched out of the complete laminate in the desired sizes (e.g. 10 cm², 20 cm², 30 cm²) and sealed into pouches under the flow of nitrogen.

5 Only approx. 95 % of the rotigotine contained in the matrix were released after 3 hours in the drug dissolution test according to the Paddle over Disk method as described in the USP using the conditions as described above. Thus, the obtained TDS contained approx. 5 % (w/w) of protonated
0 rotigotine.

The mean size of the microreservoirs in the TDS was approx. 15 µm with typical sizes in the range of 10 to 20 µm.

5 COMPARATIVE EXAMPLE 2 (high salt content, large
0 microreservoirs)

150 g Rotigotine hydrochloride were added to a solution of 17.05 g NaOH in 218 g ethanol (96%). The resulting mixture
0 was stirred for approximately 10 minutes. Then 23.7 g of sodium phosphate buffer solution (8.35 g Na₂HPO₄·2H₂O and 16.07 g NaH₂PO₄·2H₂O in 90.3 g water) was added. Insoluble or precipitated solids were separated from the mixture by filtration. The filter was rinsed with 60.4 g ethanol (96 %)
5 to obtain a particle-free ethanolic solution of rotigotine essentially in the form of the free base.

The rotigotine solution (346.4 g) in ethanol (35 % w/w) was mixed with 36.2 g ethanol (96%). The resulting solution was mixed with 109 g of an ethanolic solution containing 25 wt% polyvinylpyrrolidone (KOLLIDON[®] 90F), 0.077 wt% aqueous sodium bisulfite solution (10 wt%), 0.25 wt% ascorbyl palmitate, and 0.63 wt% DL-alpha-tocopherol until homogenous. To the mixture, 817.2 g of an amine resistant high tack silicone adhesive (BIO-PSA[®] Q7-4301 mfd. by Dow Corning) (74 wt% solution in heptane), 851.8 g of an amine resistant medium tack silicone adhesive (BIO-PSA[®] Q7-4201 mfd. by Dow Corning) (71 wt% solution in heptane), and 205.8 g petrol ether (heptane) were added, and all components were stirred until a homogenous dispersion was obtained.

5 The dispersion was coated onto a suitable polyester release liner (SCOTCHPAK[®] 1022) with a suitable doctor knife and the solvents were continuously removed in a drying oven at temperatures up to 80°C for about 30 min to obtain a drug-containing adhesive matrix of 50 g/m² coating weight. The 0 dried matrix film was laminated with a polyester-type backing foil (SCOTCHPAK[®] 1109). The individual patches were punched out of the complete laminate in the desired sizes (e.g. 10 cm², 20 cm², 30 cm²) and sealed into pouches under the flow of nitrogen.

5 Owing to the large microreservoirs in the TDS' matrix, it was possible to dissolve the rotigotine salts by direct contact with the dissolution medium. Thus, it was not possible to determine the amount of the protonated form of rotigotine. 0 This indicates that the maximum diameter of the microreservoirs was larger than the thickness of the matrix.

The mean size of the microreservoirs in the TDS was approx. 50 µm with typical sizes in the range of 20 to 90 µm. A 5 microscope image of the obtained TDS is shown in Fig. 4.

As rotigotine was released from rotigotine hydrochloride in a manner similar to Comparative Example 1, one may conclude that the obtained TDS also contained 5 % (w/w) of rotigotine in its protonated form.

5

COMPARATIVE EXAMPLE 3 (Acrylate-type formulation)

A mixture of 50.0 g rotigotine hydrochloride and 28.6 g sodium trisilicate in 95 g methyl ethyl ketone was stirred at 10 room temperature for 48 hours. Subsequently, 17.9 g oleic alcohol, 128.6 g of an acrylic-type adhesive solution (51.4 % w/w in ethyl acetate; trade name: Durotak® 387-2287 from NATIONAL STARCH & CHEMICAL), 33.0 g of EUDRAGIT® E100 (from ROEHM PHARMA) (50 % w/w solution in ethyl acetate) and 15 45.0 g ethyl acetate were added, and the mass was homogenised mechanically.

The dispersion was coated onto a suitably siliconised process liner (Hostaphan® RN 100), and the solvents were evaporated 20 at 50°C over 30 minutes, thereby obtaining a matrix weight of 60 g/m². The dry film was laminated with a suitable polyester foil (Hostaphan® RN 15). Individual patches having a desired size of (e.g. 20 cm²) were punched out of the resulting laminate and sealed into pouches under the flow of nitrogen.

25

EXAMPLE 2

In vivo drug absorption test

In order to monitor the absorption of the amine functional 30 drug by the human skin the following experiment was carried out. The test was performed with the TDS obtained in Example 1 as well as in Comparative Examples 1 and 2.

The plasma concentration time profile at different test times 35 was determined in pharmacokinetic studies involving (A) 14 healthy male persons (TDS of Comparative Examples 2 and 3) or (B) 30 healthy male persons (TDS of Example 1 and Comparative

Example 1), respectively. The studies were conducted following an open single-dose randomised (B) two-way or (A) three-way cross-over design.

5 Individual concentrations of rotigotine were determined by means of liquid chromatography and mass spectroscopy. The lower limit of quantification (LOQ) was 10 pg/ml.

The drug absorption was calculated from the plasma
0 concentration data according to the Wagner-Nelson method
(Malcom Rowland, Thomas N. Tozer (Eds.) "Estimation of
Adsorption Kinetics from Plasma Concentration Data" in
Clinical Pharmacokinetics, pp 480-483, Williams & Wilkins,
1995), 100 % = absorption rate after 48 hours; patch
.5 application time was 24 hours.

A comparison of the flux across human skin for the different TDS tested is shown in Fig. 1, 2 and 3.

30 In Fig. 1 the rotigotine absorption for the sample obtained in Example 1 containing no salt (O) is compared to the sample obtained in Comparative Example 1 containing approx. 5 % (w/w) of rotigotine hydrochloride (●). The comparison in Fig. 1 clearly shows that the drug absorption after patch application depends on the residual salt content in the semi-permeable matrix and is significantly improved by reducing the amount of the protonated form of the amine-functional drug present in the matrix.

35 Fig. 2 shows the impact of the size distribution of the microreservoirs distributed in the semi-permeable matrix by comparing the sample obtained in Comparative Example 1 having a mean microreservoir size of approx. 15 µm and typical sizes between 10 and 20 µm (●) with the sample obtained in Comparative Example 2 having a mean microreservoir size of approx. 50 µm and typical sizes between 20 and 90 µm (▲). From this comparison it can be deduced that reducing the size

of the matrix reservoirs significantly increases the flux across the human skin.

5 A comparison between the TDS of Example 1 (O) and Comparative Example 2 (▲) is shown in Fig. 3. This comparison clearly indicates that the flux across human skin is significantly enhanced by reducing the salt content and decreasing the size of the microreservoirs.

.0 EXAMPLE 3

In vitro Diffusion Experiment with transdermal drug delivery systems

.5 The test was performed with a sandwich of consecutively a supportive separator membrane, skin and the TDS. Active substance that has diffused from the TDS through the skin and/or membrane dissolves in an acceptor liquid that continuously passes directly underneath the membrane; the acceptor liquid was collected in tubes in a fraction collector; and the fractions were analysed for their content of rotigotine. The flux of active substance through skin was calculated by correcting for the influence of the separator membrane.

20 25 The diffusion cell described in Tanojo et al. (Tanojo et al. "New design of a flow through permeation cell for in vitro permeation studies across biological membranes" Journal of Controlled Release (1997), 45, 41-47) was used in order to conduct the experiment.

30 A flask containing the acceptor liquid and the assembled diffusion cells were placed in a temperature-controlled water-bath (32.0 ±0.5 °C). The acceptor liquid was continuously pumped from the flask through PTFE tubing by a 35 peristaltic pump, passed through the diffusion cells where the diffusion takes place and was then transported via PTFE

tubing to test tubes that were placed in a fraction collector.

The required number of disks was punched out from the TDS by 5 using a circular knife. Human epidermis, excised to a thickness of 200-300 μm from fresh donor skin (storage ≤ 36 hours at 4°C) with a dermatome (to be referred to as skin) was spread out on laboratory film in petridishes.

Using the circular knife the required number of disks was 10 punched out. A disk of membrane was centred on each cell surface. The skin disks were spread out on the membrane disks on the cell surfaces with the aid of forceps. A disk of the TDS is applied to each cell, and the cells were assembled. The experiment was then conducted in a manner 15 similar to the one described in Tanojo et al above.

Afterwards the tubes containing the collected fraction were weighed, and the contents of each tube were analysed using HPLC.

20 This experiment was carried out for the TDS of Example 1 as well as Comparative Examples 2 and 3.

Fig. 6 shows the in vitro skin permeation profile for the TDS 25 of Example 1 (●) compared to the TDS of Comparative Example 2 (○).

Fig. 7 shows the in vitro skin permeation profile for the TDS 30 of Example 1 (●) compared to the acrylate TDS of Comparative Example 3 (○).

It is clear from the data obtained that the flux across human skin may be significantly enhanced by controlling the size of the microreservoirs in the TDS while at the same time 35 providing a semi-permeable matrix, which is highly permeable for the free base of the amine functional drug while being impermeable for its protonated form.

CLAIMS

1. A transdermal delivery system (TDS) comprising a backing layer inert to the components of the matrix, a self-adhesive matrix containing an amine-functional drug and a protective foil or sheet to be removed prior to use,

5 characterized in that

.0 the self-adhesive matrix consists of a solid or semi-solid semi-permeable polymer

.5 (1) wherein an amine functional drug in its free base form has been incorporated,

.5 (2) which is saturated with the amine functional drug and contains said drug as a multitude of microreservoirs within the matrix,

.0 (3) which is highly permeable for the free base of the amine functional drug,

.0 (4) which is impermeable for the protonated form of the amine functional drug,

.5 (5) wherein the maximum diameter of the microreservoirs is less than the thickness of the matrix.

25 2. The TDS according to claim 1, characterized in that the mean diameter of the microreservoirs is in the range of 0.5 to 20 μm .

30 3. The TDS according to claim 1 or 2, characterized in the amine functional drug having an octanol/water partitioning coefficient $\log P \geq 2.8$ at pH 7.4.

35 4. The TDS according to any one of claims 1 to 3, characterized in the amine functional drug having a pK_a of 7.4 to 8.4.

5. The TDS according to any one of claims 1 to 4, characterized in that the amine functional drug is a dopamine D2 receptor agonist.
- 5 6. The TDS according to claim 5, characterized in that the dopamine D2 receptor agonist is an aminotetraline compound.
- 10 7. The TDS according to claim 6, characterized in that the aminotetraline compound is rotigotine.
8. The TDS according to claim any one of claims 1 to 4, characterized in that the amine-functional drug is an anticholinergic drug.
- 15 9. TDS according to claim 8, characterized in that the anticholinergic drug is oxybutynine.
- 20 10. The TDS according to any one of the preceding claims, characterized in the self-adhesive matrix being free of particles that can absorb salts of the amine functional drug at the TDS/skin interface.
- 25 11. The TDS according to any of the preceding claims, characterized in that the polymer matrix comprises a silicone-type pressure sensitive adhesive.
- 30 12. The TDS according to any of the preceding claims, characterized in that the polymer matrix comprises two or more silicone-type pressure sensitive adhesives as the main adhesive components.
- 35 13. The TDS according to claim 12, wherein the silicone type pressure sensitive adhesive is a blend of a high tack silicone type pressure sensitive adhesive comprising polysiloxane with a resin and a medium tack silicone

type pressure sensitive adhesive comprising polysiloxane with a resin.

14. Method for treatment of a patient suffering from a
5 disease treatable by an amine functional drug by applying the TDS according to any one of claims 1 to 13 to the skin of the patient.

Fig. 1

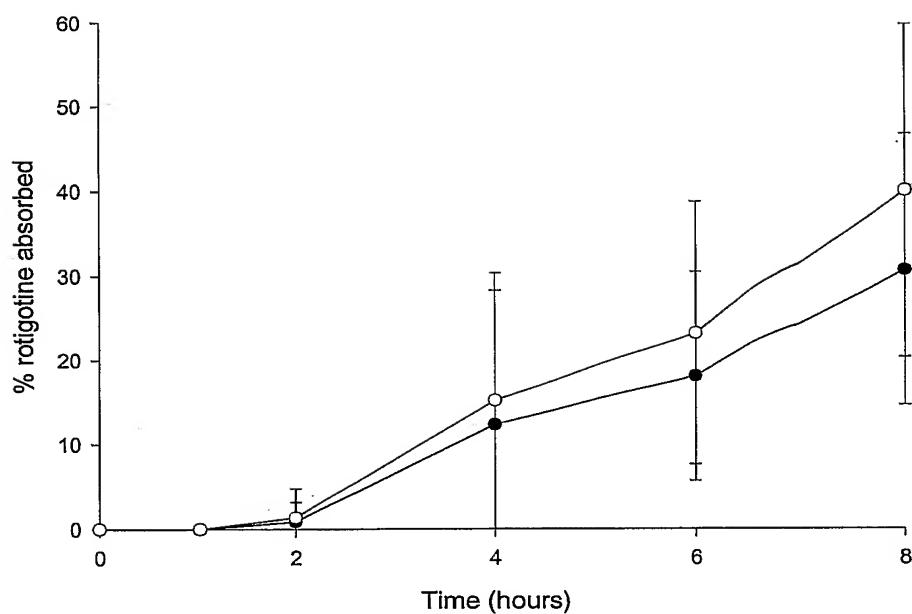
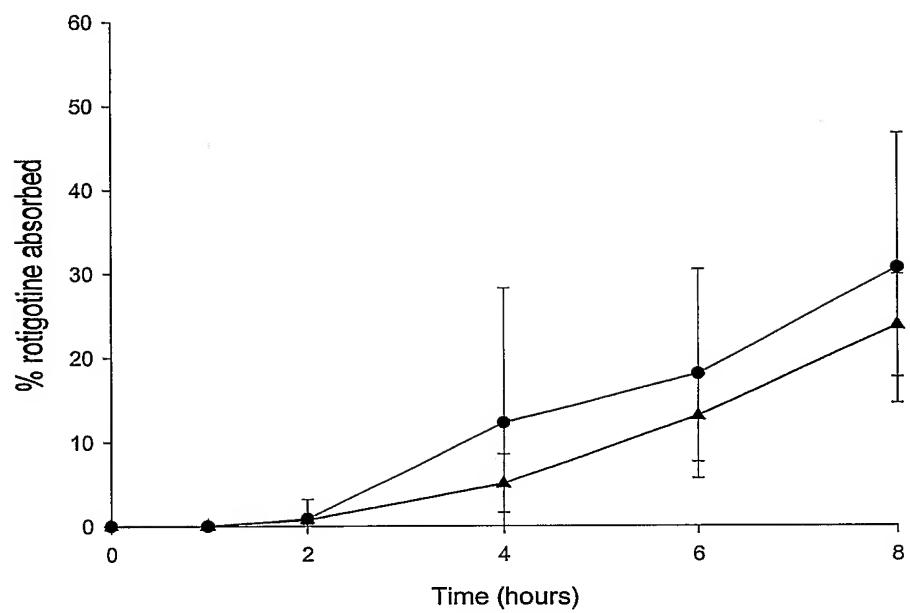


Fig. 2



3/7

Fig. 3

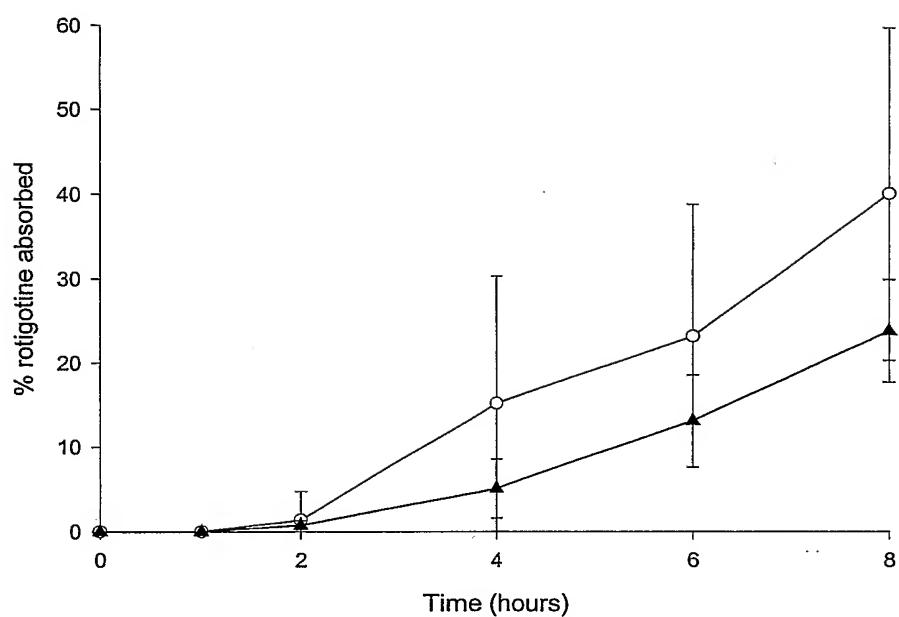


Fig. 4

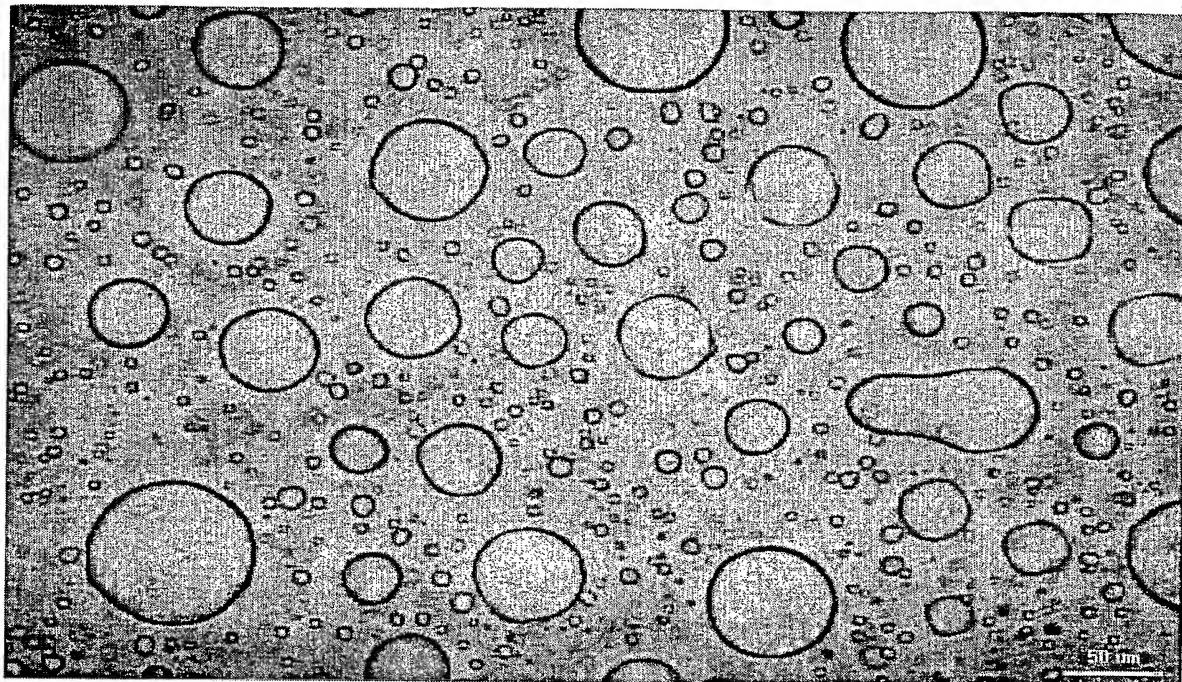
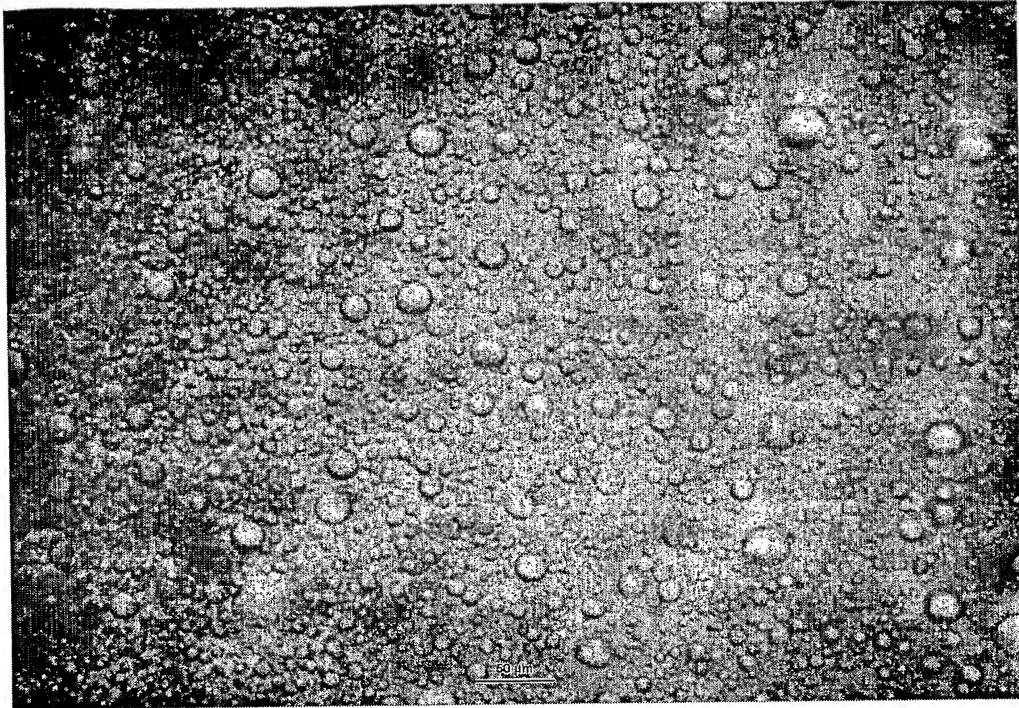


Fig. 5



6/7

Fig. 6

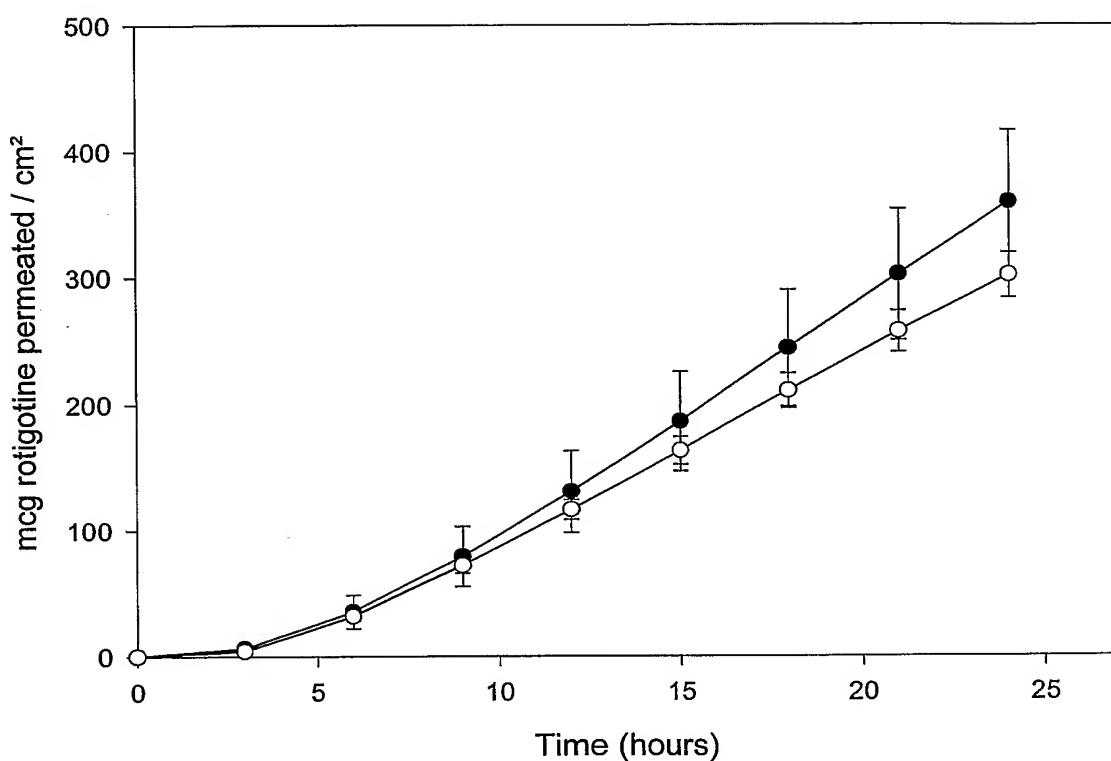
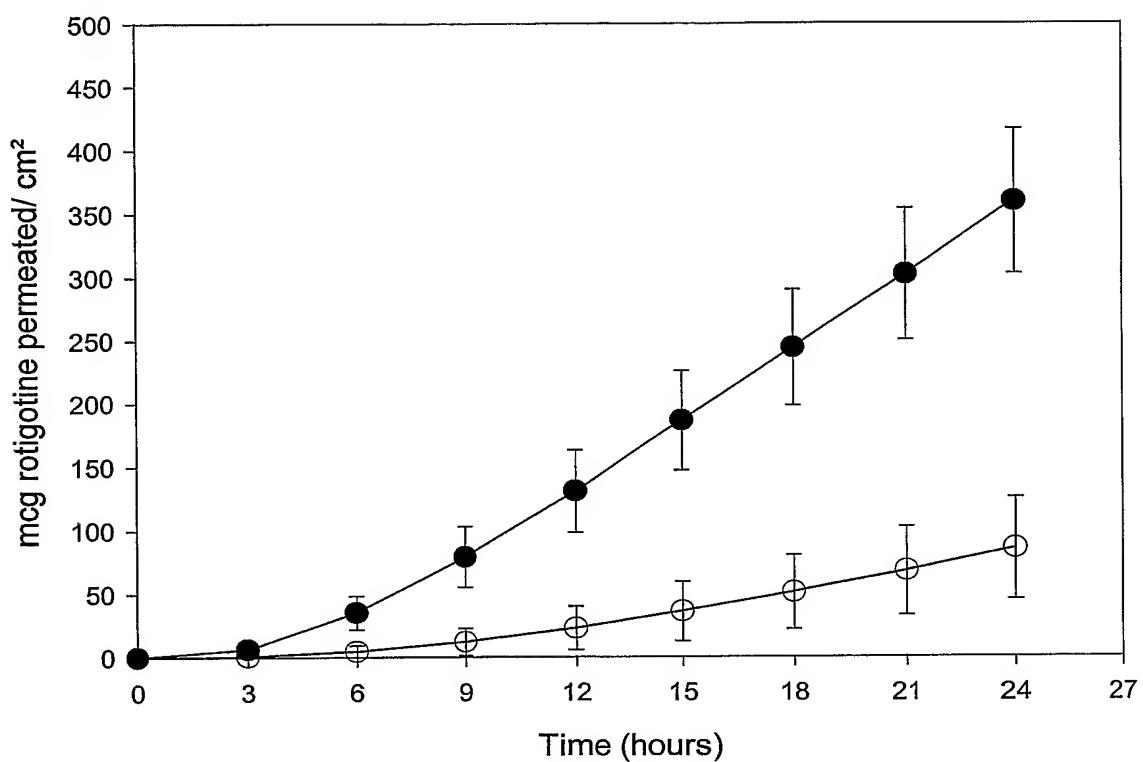


Fig. 7



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08319

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 07468 A (CYGNUS THERAPEUTIC SYSTEMS) 14 April 1994 (1994-04-14) cited in the application page 1, line 23,24; claims 1,12,14; examples 15,16 page 7 -page 8 ---	1,5-7, 11,14
X	WO 99 49852 A (LOHMANN THERAPIE SYST LTS ;MUELLER WALTER (DE); PECK JAMES V (US);) 7 October 1999 (1999-10-07) page 4, paragraph 2; claims 1,6,13 page 5, paragraph 2 ---	1,5-7, 11,14
X	DE 198 14 083 A (LOHMANN THERAPIE SYST LTS) 14 October 1999 (1999-10-14) claims 1,13,14; examples 1-3 ---	1,5,14 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

18 December 2003

Date of mailing of the international search report

30/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kardas-Llorens, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08319

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 834 010 A (VENKATESHWARAN SRINIVASAN ET AL) 10 November 1998 (1998-11-10) column 3, line 35-65; claims 1-7,19 column 7, line 36-55 ---	1,4-6,8, 9,11,14
X	WO 98 00126 A (SEPRACOR INC) 8 January 1998 (1998-01-08) page 1; claims 5,9 ---	1,5,6,8, 9,14
X	DE 100 60 550 C (LOHMANN THERAPIE SYST LTS) 18 April 2002 (2002-04-18) see paragraphs 0024,0025,0026,0032 Claim 1 ---	1,5,6, 8-12,14
X	US 5 601 839 A (QUAN DANYI ET AL) 11 February 1997 (1997-02-11) column 5 -column 6; claims 1,12; example 1 ---	1,4-6,8, 9,11,14
X	FR 2 792 529 A (SOD CONSEILS RECH APPLIC) 27 October 2000 (2000-10-27) page 1, line 22; claims 3,8-10; examples 1,2 ---	1,6,14
Y	ROY S D ET AL: "CONTROLLED TRANSDERMAL DELIVERY OF FENTANYL: CHARACTERIZATIONS OF PRESSURE-SENSITIVE ADHESIVES FOR MATRIX PATCH DESIGN" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 85, no. 5, 1 May 1996 (1996-05-01), pages 491-495, XP000583527 ISSN: 0022-3549 see all pages ---	1
Y	ROY S D ET AL: "TRANSDERMAL DELIVERY OF NARCOTIC ANALGESICS: PH, ANATOMICAL, AND SUBJECT INFLUENCES ON CUTANEOUS PERMEABILITY OF FENTANYL AND SUFENTANIL" PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 7, no. 8, 1990, pages 842-847, XP002923066 ISSN: 0724-8741 see all pages ---	1
E	EP 1 256 340 A (LOHMANN THERAPIE SYST LTS ; SANOL ARZNEI SCHWARZ GMBH (DE)) 13 November 2002 (2002-11-13) see paragraphs 0014, 0029, 0037 claims 1,8 ---	1,5-7, 10,11,14
E	WO 02 074286 A (ALZA CORP) 26 September 2002 (2002-09-26) see paragraphs 00053,00056, 00098 claims 1,25-28,32-35 ---	1,5,6, 11,14

-/-

INTERNATIONAL SEARCH REPORTInternational Application No
PCT/EP 03/08319**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 26217 A (3M INNOVATIVE PROPERTIES CO ;CANTOR ADAM S (US); OCHELTREE TERRANC) 4 April 2002 (2002-04-04) page 9, line 15-30; claims 1,30-33; examples 1-54 -----	1,5,6, 11,12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08319

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.1

Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08319

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
WO 9407468	A 14-04-1994	US	5989586 A		23-11-1999
		AT	198420 T		15-01-2001
		AU	5321194 A		26-04-1994
		CA	2145631 A1		14-04-1994
		CN	1089469 A		20-07-1994
		DE	69329825 D1		08-02-2001
		DE	69329825 T2		13-06-2001
		DK	662822 T3		29-01-2001
		EP	0662822 A1		19-07-1995
		ES	2155073 T3		01-05-2001
		GR	3035626 T3		29-06-2001
		JP	8504757 T		21-05-1996
		PT	662822 T		30-04-2001
		WO	9407468 A1		14-04-1994
		US	5840336 A		24-11-1998
WO 9949852	A 07-10-1999	DE	19814084 A1		14-10-1999
		AT	210973 T		15-01-2002
		AU	746856 B2		02-05-2002
		AU	2934199 A		18-10-1999
		BR	9909313 A		21-11-2000
		CA	2326630 A1		07-10-1999
		CN	1295470 T		16-05-2001
		DE	59900581 D1		31-01-2002
		DK	1033978 T3		15-04-2002
		WO	9949852 A1		07-10-1999
		EP	1033978 A1		13-09-2000
		ES	2170573 T3		01-08-2002
		HK	1031196 A1		10-05-2002
		HU	0101519 A2		28-09-2001
		JP	2002509878 T		02-04-2002
		NO	20004915 A		08-11-2000
		NZ	507066 A		31-01-2003
		PL	343255 A1		30-07-2001
		PT	1033978 T		28-06-2002
		SI	1033978 T1		31-10-2002
		SK	14462000 A3		09-04-2001
		TR	200002829 T2		22-01-2001
		ZA	200005261 A		22-05-2001
DE 19814083	A 14-10-1999	DE	19814083 A1		14-10-1999
		AT	241343 T		15-06-2003
		AU	758291 B2		20-03-2003
		AU	3597499 A		18-10-1999
		CA	2326660 A1		07-10-1999
		DE	59905750 D1		03-07-2003
		WO	9949844 A2		07-10-1999
		EP	1067916 A2		17-01-2001
		JP	2002509874 T		02-04-2002
		NO	20004926 A		22-11-2000
		US	6620429 B1		16-09-2003
US 5834010	A 10-11-1998	US	5601839 A		11-02-1997
		AT	205694 T		15-10-2001
		AU	696777 B2		17-09-1998
		AU	5446796 A		18-11-1996
		CA	2217888 A1		31-10-1996
		CN	1182358 A		20-05-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08319

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 5834010	A		DE 69615399 D1 DE 69615399 T2 DK 871420 T3 EP 0871420 A1 ES 2163012 T3 JP 3228341 B2 JP 10507199 T JP 2001039865 A KR 275593 B1 NZ 306249 A PT 871420 T WO 9633678 A1 ZA 9603229 A	25-10-2001 30-01-2003 21-01-2002 21-10-1998 16-01-2002 12-11-2001 14-07-1998 13-02-2001 15-12-2000 27-03-2000 28-03-2002 31-10-1996 28-01-1997
WO 9800126	A	08-01-1998	US 5736577 A AU 732568 B2 AU 3513797 A BR 9710031 A CA 2257121 A1 CZ 9804283 A3 EP 0914113 A1 HU 9903839 A2 JP 2000513724 T KR 2000022194 A NO 985896 A NZ 333282 A PL 330752 A1 RU 2195276 C2 SK 178698 A3 WO 9800126 A1	07-04-1998 26-04-2001 21-01-1998 10-08-1999 08-01-1998 16-06-1999 12-05-1999 28-03-2000 17-10-2000 25-04-2000 16-12-1998 23-06-2000 24-05-1999 27-12-2002 10-09-1999 08-01-1998
DE 10060550	C	18-04-2002	DE 10060550 C1 AU 3452502 A WO 0245699 A2 EP 1347749 A2	18-04-2002 18-06-2002 13-06-2002 01-10-2003
US 5601839	A	11-02-1997	AT 205694 T AU 696777 B2 AU 5446796 A CA 2217888 A1 CN 1182358 A DE 69615399 D1 DE 69615399 T2 DK 871420 T3 EP 0871420 A1 ES 2163012 T3 JP 3228341 B2 JP 10507199 T JP 2001039865 A KR 275593 B1 NZ 306249 A PT 871420 T WO 9633678 A1 US 5834010 A ZA 9603229 A	15-10-2001 17-09-1998 18-11-1996 31-10-1996 20-05-1998 25-10-2001 30-01-2003 21-01-2002 21-10-1998 16-01-2002 12-11-2001 14-07-1998 13-02-2001 15-12-2000 27-03-2000 28-03-2002 31-10-1996 10-11-1998 28-01-1997
FR 2792529	A	27-10-2000	FR 2792529 A1 AU 4304400 A	27-10-2000 10-11-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/08319

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
FR 2792529	A		CA 2370581 A1 EP 1173173 A1 WO 0064444 A1 JP 2002542290 T	02-11-2000 23-01-2002 02-11-2000 10-12-2002
EP 1256340	A	13-11-2002	EP 1256340 A1 AT 246919 T DE 60100595 D1 DK 1256340 T3 WO 02089777 A1 EP 1325742 A1 US 2003027793 A1 ZA 200209980 A	13-11-2002 15-08-2003 18-09-2003 01-12-2003 14-11-2002 09-07-2003 06-02-2003 24-02-2003
WO 02074286	A	26-09-2002	CA 2440884 A1 WO 02074286 A1 US 2003026829 A1	26-09-2002 26-09-2002 06-02-2003
WO 0226217	A	04-04-2002	AU 1531502 A BR 0114315 A CA 2423836 A1 CZ 20030890 A3 EP 1322299 A2 NO 20031165 A WO 0226217 A2 US 2002119187 A1	08-04-2002 14-10-2003 04-04-2002 17-09-2003 02-07-2003 26-05-2003 04-04-2002 29-08-2002